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Dimethoxypyrimidines as Novel Herbicides. Part 4. Quantitative Structure–Activity Relationships of Dimethoxypyrimidinyl(thio)salicylic Acids‡

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Abstract: The activity of a number of *O*-(4,6-dimethoxypyrimidin-2-yl)salicylic acids and their thio analogs inhibiting acetolactate synthase (ALS) preparation was measured. The effects of substituents on the salicylic-benzene ring on the inhibitory activity were analyzed quantitatively with physicochemical substituent parameters. For 6-substituted (thio)salicylic acids, the activity was shown to vary parabolically with the 'intramolecular' steric parameter ($\mathbf{E_s}$). In addition, the higher steric dimension of substituents in terms of the STERIMOL width or length parameter lowered the activity. The field-inductive electron-withdrawing property of the 6-substituents in terms of the Swain–Lupton–Hansch **F** was favorable for the activity of salicylic acid series. In 5-substituted salicylic acids, the activity was increased by electron-donating substituents with smaller size. The relationships between ALS inhibitory and herbicidal activities were also analyzed with some weed species. Both pre- and post-emergence activities against barnyard grass, *Echinochloa crus-galli*, were linearly related to the ALS inhibitory activity after allowing for the hydrophobic factor that may contribute to the transport processes. Those against two broad-leaved weed species, *Polygonum convolvulus* and *Abutilon theophrasti* were linearly related to the in-vitro activity with no significant participation of the hydrophobic factor. © 1998 SCI

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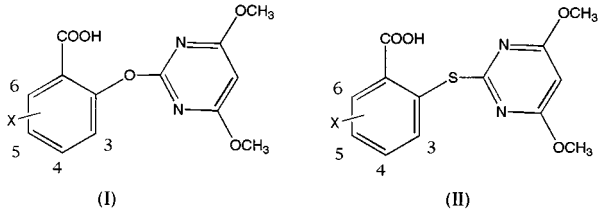
Key words: dimethoxypyrimidines; herbicide; structure–activity relationship; salicylic acids

1 INTRODUCTION

Certain *O*-(4,6-dimethoxypyrimidin-2-yl)salicylic acids (Fig. 1; **I**) and their thio analogs (**II**) show potent herbi-



(I) (II)

Fig. 1. The general structures of *O*-(4,6-dimethoxypyrimidin-2-yl)salicylic acids (**I**) and thio analogues (**II**).

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cidal activity.[1] The activity is believed to be due to the inhibition of acetolactate synthase (ALS) which participates in the synthesis of branched-chain amino acids in the plant body.[1] The effect of substituents X introduced into various positions of the benzene ring is striking. Some substituents at the 6-position increase the ALS inhibitory activity enormously, whereas others, as well as most substituents at the other positions, have the reverse effect.[1] The replacement of O in oxy-(**I**) with S in the thio-series (**II**), with substituent(s) kept unchanged, however, does not much affect ALS inhibition except for a few pairs of analogs. The phytotoxicity of salicylic acids (**I**) is, however, reduced, in general, in the corresponding thiosalicylic acids (**II**). The extent of the toxicity reduction varies depending on the crop/weed species, leading to selectively herbicidal thiosalicylic acids.

The purpose of the present study is to understand the physicochemical background of substituent effects on the ALS inhibitory and herbicidal potency variations in the two series of compounds **I** and **II**. We have analyzed the effect of substituents, X, on the (thio)salicylic acid-benzene ring on the ALS inhibitory activity measured with an enzyme preparation from pea seedlings (*Pisum sativum* L. var. Alaska). We have also analyzed possible relationships of the ALS inhibition with herbicidal potency for several weed species. The analyses have been made quantitatively with physicochemical substituent and/or molecular parameters and regression analyses (QSAR).[2,3] Here, we report the details of these QSAR analyses.

2 MATERIALS AND METHODS

2.1 Compounds

Many of pyrimidinyl-salicylic and -thiosalicylic acids were of the same samples as those previously reported.[1] Others were prepared in ways similar to previous compounds.[1] The structure of new compounds was confirmed by NMR, IR, and mass spectrometric methods. Melting point (m.p.) or refractive index (n_D^{20}) of compounds is indicated in Tables 1–4.

TABLE 1
ALS Inhibitory Activity and Physicochemical Substituent Parameters of 6-Substituted *S*-Pyrimidinyl-thiosalicylic Acids (**II**)

			pI_{50}						
No.[a]	*Substituent*	*m.p.*(°*C*)	*Obs.*	*Calc.*[b]	$\lvert\Delta\rvert$	E_s[c]	ΔL[d]	ΔB_5[d]	F[d]
1*	H	127–130	6·80	7·07	0·27	0·00	0·00	0·00	0·00
2	F	133–135	7·67	7·51	0·16	−0·46	0·59	0·35	0·45
3	Cl	148–151	7·49	7·43	0·06	−0·97	1·46	0·80	0·42
4	Br	164–165	7·40	7·29	0·11	−1·16	1·76	0·95	0·45
5	I	159–163	6·99	7·00	0·01	−1·40	2·17	1·15	0·42
6	CH_3	131–132	7·53	7·70	0·17	−1·24	0·81	1·04	0·01
7	OCH_3	168–170	7·05	6·98	0·07	−0·55	1·92	2·07	0·29
8	OC_2H_5	157–160	6·70	6·61	0·09	−0·55	2·74	2·36	0·26
9	OC_3H_7	125–128	6·14	6·03	0·11	−0·55	3·99	3·42	0·26
10	$OCH(CH_3)_2$	113–115	4·88[e]	6·61	1·73	−0·55	2·74	3·10	0·34
11*	OC_6H_5	98–100	5·60[e]	6·74	1·14	−0·55	2·45	4·89	0·37
12	SCH_3	145–147	7·68	7·08	0·60	−1·07	2·24	2·26	0·23
13	SC_2H_5	141–143	6·67	6·68	0·01	−1·07	3·10	2·97	0·26
14*	SC_3H_7	108–111	5·72	6·19	0·47	−1·07	4·15	3·98	0·26
15	CF_3	195–198	6·02	5·84	0·18	−2.40	1·24	1·61	0·38
16	NO_2	190–192	6·69	7·14	0·45	−1·65[f]	1·38	1·44	0·65
17	$COCH_3$	177–180	7·14	7·18	0·04	−0·95[g]	2·00	2·13	0·33
18*	COC_6H_5	135–139	5·19[e]	6·95	1·76	−1·06[g]	2·51	4·98	0·31

[a] Newly synthesized compounds are asterisked.
[b] Calculated by eqn (4).
[c] Unless noted, taken from Refs 9 and 10.
[d] Taken from Refs 11 and 12. The reference point of **L** and $\mathbf{B_5}$ values is shifted to that of H [$\mathbf{B_5}$(H) = 1.00, **L**(H) = 2·06].
[e] Omitted from the analyses.
[f] Taken from Ref. 13.
[g] Taken from Ref. 15. The $\mathbf{E_s}$ value is estimated from the correlation equation for the *N*-quaternary-methylation rate constant of *ortho*-substituted *N*,*N*-dimethylanilines with methyl iodide. The steric effect is separated from the 'ordinary' and 'proximity' electronic effects using congeners having *ortho* substituents, the $\mathbf{E_s}$ and **F** (or σ_I) values of which are known (see Ref. 18).

TABLE 2
ALS Inhibitory Activity and Physicochemical Substituent Parameters of 6-Substituted *O*-Pyrimidinylsalicylic Acids (**I**)

			pI_{50}						
No.[a]	*Substituent*	*m.p.*(°C) *or* n_D^{20}	*Obs.*	*Calc.*[b]	$\|\Delta\|$	E_s[c]	ΔL[d]	ΔB_5[d]	F[d]
19	H	150–152	6·64	6·65	0·01	0·00	0·00	0·00	0·00
20	F	133–134	7·30	7·78	0·48	−0·46	0·59	0·35	0·45
21	Cl	123–126	7·62	7·83	0·21	−0·97	1·46	0·80	0·42
22	Br	136–138	7·82	7·86	0·04	−1·16	1·76	0·95	0·45
23	I	138–141	7·66	7·72	0·06	−1·40	2·17	1·15	0·42
24	CH_3	119–120	6·89	7·07	0·18	−1·24	0·81	1·04	0·01
25	C_2H_5	122–123	6·57	6·68	0·11	−1·31	2·05	2·17	0·00
26	C_3H_7	1·5419	5·89	6·51	0·62	−1·60	2·86	2·49	0·01
27	OCH_3	138–140	7·36	7·00	0·36	−0·55	1·92	2·07	0·29
28	OC_2H_5	127–128	7·05	6·86	0·19	−0·55	2·74	2·36	0·26
29	OC_3H_7	110–111	6·24	6·51	0·27	−0·55	3·99	3·42	0·26
30	$OCH(CH_3)_2$	120–122	5·73[e]	6·75	1·02	−0·55	2·74	3·10	0·34
31	OC_4H_9	107–108	6·21	6·44	0·23	−0·55	4·80	3·79	0·29
32	$OCHF_2$	113–115	7·19	6·96	0·23	−0·55	1·92	2·61	0·37
33*	OC_6H_5	116–118	7·70[e]	6·22	1·48	−0·55	2·45	4·89	0·37
34	SCH_3	139–142	7·57	7·04	0·53	−1·07	2·24	2·26	0·23
35	SC_2H_5	103–104	7·11	6·86	0·25	−1·07	3·10	2·97	0·26
36	SC_3H_7	93–96	6·29	6·53	0·24	−1·07	4·15	3·98	0·26[f]
37	CF_3	151–153	6·96	6·74	0·22	−2·40	1·24	1·61	0·38
38	NO_2	125–128	6·64	7·10	0·46	−2·52[g]	1·38	1·44	0·65
39	CO_2CH_3	1.5541	5·68[e]	6·48	0·80	−2·36[g]	2·67	2·36	0·34
40	$COCH_3$	163–165	6·84	6·53	0·31	−2·36[g]	2·00	2·13	0·33
41	COC_6H_5	166–168	5·67	5·56	0·11	−2·36[g]	2·51	4·98	0·31
42	C_6H_5	129–131	7·80	7·35	0·45	−1·01[h]	4·22	0·71[i]	0·12
43	1-Pyrryl	125–127	8·28	8·01	0·27	−1·01[h]	3·38	0·71[i]	0·50
44*	CH_3SO_2	148–151	5·87	5·81	0·06	−3·02[g]	2·05	2·17	0·53
45	NH_2	149–152	7·00	7·04	0·04	−0·61	0·72	0·97	0·08

[a] Newly synthesized compounds are asterisked.
[b] Calculated using eqn (8).
[c] Unless noted, taken from Refs 9 and 10.
[d] Taken from Refs 11 and 12.
[e] Omitted from the analyses.
[f] Taken as that of SC_2H_5.
[g] E_s for the 'half-width', see text.
[h] E_s for the half-thickness.
[i] Corresponds with the half-thickness.

2.2 Inhibition of ALS preparation

With the procedure reported previously,[4] the ALS sample was prepared from six- to seven-day-old etiolated pea shoots. The molar concentration required for 50% inhibition (I_{50}) of the ALS activity was evaluated for each compound by the probit method.[5] Molar pI_{50} values, the log of the reciprocal I_{50}, are listed in Tables 1–4.

2.3 Herbicidal assay

Pre- and post-emergence herbicidal activities were measured by the previously reported method,[5–7] but more precisely, so that the activities of each compound were expressible in terms of the ED_{90} value, the rate (mole ha^{-1}) of the active ingredient required for 90% damage of seedlings of weed species. For post-emergence activity, the damage was evaluated two weeks after the application of each herbicide to seedlings of one-leaf or two-leaf stage. For the pre-emergence test, the activity was evaluated two weeks after the application which was made immediately after sowing. The results are shown in Table 4.

2.4 Hydrophobicity parameter

The log P (1-octanol/water) value was used as the parameter for molecular hydrophobicity. For most

TABLE 3
ALS Inhibitory Activity and Physicochemical Substituent Parameters of 5-Substituted *O*-Pyrimidinylsalicylic Acids (**I**)

No.[a]	*Substituent*	*m.p.*(°C)	pI_{50}			σ_m[c]	σ_p[c]	ΔL[c]	ΔB_5[c]
			Obs.	*Calc.*[b]	$\lvert\Delta\rvert$				
19	H	150–152	6·64	6·28	0·36	0·00	0·00	0·00	0·00
46	F	118–121	6·27	5·79	0·48	0·34	0·06	0·59	0·35
47	Cl	130–132	5·35	4·98	0·37	0·37	0·23	1·46	0·80
48	Br	141–144	4·50	4·77	0·27	0·39	0·23	1·76	0·95
49	I	164–167	5·05	4·55	0·50	0·35	0·18	2·17	1·15
50	CH_3	159–162	5·03	5·69	0·66	−0·07	−0·17	0·81	1·04
51*	C_2H_5	141–143	4·59	4·62	0·03	−0·07	−0·15	2·05	2·17
52	OCH_3	157–159	4·60	4·86	0·26	0·12	−0·27	1·92	2·07
53*	OC_6H_5	142–144	3·58	3·32	0·26	0·25	−0·03	2·45	4·89
54*	SCH_3	148–152	4·32	4·32	0·00	0·15	0·00	2·24	2·26
55*	CN	141–144	3·71	4·19	0·48	0·56	0·66	2·17	0·60
56*	NH_2	153–156	6·09	6·32	0·23	−0·16	−0·66	0·72	0·97
57*	C≡CH	146–148	4·70	4·46	0·24	0·21	0·23	2·60	0·60
58*	NO_2	127–131	3·90	4·17	0·27	0·71	0·78	1·38	1·44
59*	OH	173–175	7·20[d]	6·02	1·18	0·12	−0·37	0·68	0·93

[a] Newly synthesized compounds are asterisked.
[b] Calculated from eqn (9).
[c] Taken from Refs 11 and 12.
[d] Omitted from the correlation.

compounds in Table 4, the log P value was estimated from the log k' value.[8] k' is the capacity factor for the reversed phase HPLC analysis at 36°C using a YMC-OPS AM-302 column (4·6 × 150 mm). [Mobile phase: acetonitrile + aqueous solution (45 + 55 by volume); aqueous solution (1100 ml): potassium chloride (0·2 M; 275 ml) + hydrochloric acid (0·2 M; 58·3 ml) + water (766·7 ml), pH 2·17; flow rate: 1 ml min^{-1}; detector: UVD (254 nm)]. Preliminary experiments confirmed that compounds were not decomposed under these HPLC conditions. The k' value is defined according to eqn (1),

$$k' = (t_R - t_0)/t_0 \quad (1)$$

where t_R and t_0 are respectively the retention times of the test compound and acetonitrile as the unretained reference.

For some of the compounds in Table 4, the log P value was directly measured by the flask-shaking method with 1-octanol/0·1 M hydrochloric acid (pH 1).[2,3] For these compounds, the relationship between log P and log k' was shown by eqn (2).

$$\log P = 2{\cdot}74(\pm 0{\cdot}56)\log k' + 1{\cdot}18(\pm 0{\cdot}35)$$
$$n = 9,\ r = 0{\cdot}975,\ s = 0{\cdot}191,\ F = 133{\cdot}0 \quad (2)$$

In this and the following equations, n represents the number of data points, r the correlation coefficient, s the standard deviation and F the ratio of regression and residual variances. The figures in parentheses are the 95% confidence intervals. The log P values of other compounds were estimated by eqn (2).

2.5 Steric and electronic parameters

To estimate steric effects of benzene-ring substituents (X), both the Taft–Kutter–Hansch-type $\mathbf{E_s}$ value[9–11] and the Verloop STERIMOL parameters[11,12] were used. For symmetric top-type substituents such as H, CH_3, CX_3 (X: halogen atom), and $C(CH_3)_3$, Kutter and Hansch formulated eqn (3) for the relationship between the original Taft $\mathbf{E_s}$ value and (averaged van der Waals radius $\mathbf{r_v}$(ave).[10]

$$\mathbf{E_s} = 3{\cdot}484(\pm 0{\cdot}55) - 1{\cdot}839(\pm 0{\cdot}22)\mathbf{r_v}(\text{ave})$$
$$n = 6,\ r = 0{\cdot}996,\ s = 0{\cdot}132,\ F = 497{\cdot}0 \quad (3)$$

The $\mathbf{E_s}$values of hetero-atom substituents such as halogens and alkoxy, alkylthio, and amino groups were evaluated from eqn (3) using van der Waals radius of halogen, O, S, and N atoms, respectively.[10] For π-bonded planar substituents such as NO_2 and C_6H_5, a set of two $\mathbf{E_s}$ values corresponding to the half-width and half thickness is proposed for the effects toward coplanar and perpendicular directions, respectively, using their van der Waals dimensions and eqn (3).[10] For

TABLE 4
Herbicidal and ALS Inhibitory Activities, and Hydrophobic Parameter of Substituted *O*-Pyrimidinylsalicylic Acids

					Herbicidal activity pED_{90}							
					Pre-emergence				*Post-emergence*			
					Ech[d]		*Pol*[e]		*Ech*[d]		*Abu*[f]	
No.[a]	*Substituent*[b]	*log k'*[c]	*log P*[c]	pI_{50}	(*Obs.*)	(*Calc.*)[g]	(*Obs.*)	(*Calc.*)[h]	(*Obs.*)	(*Calc.*)[i]	(*Obs.*)	(*Calc.*)[j]
19	H	0·267	2·10[k]	6·64	4·14	4·70	4·44	4·96	4·44	4·98	4·74	5·15
20	6-F	0·284	1·95	7·30	5·17	5·14	5·77	5·45	5·47	5·62	5·47	5·67
21	6-Cl	0·408	2·23[k]	7·62	5·49	5·49	5·79	5·68	6·09	5·91	6·09	5·92
22	6-Br	0·441	2·38	7·82	5·85	5·65	5·85	5·83	5·85	6·03	6·15	6·07
24	6-CH_3	0·380	2·22	6·89	5·16	4·93	5·16	5·14	5·16	5·20	5·46	5·35
25	6-C_2H_5	0·571	2·74	6·57	5·18	4·56	5·48	4·90	—[l]	4·51	5·28	5·10
27	6-OCH_3	0·199	1·45[k]	7·36	5·19	4·69	5·19	5·49	5·79	5·41	5·79	5·72
28	6-OC_2H_5	0·386	2·23	7·05	5·21	5·05	5·21	5·26	5·51	5·35	5·51	5·47
29	6-OC_3H_7	0·599	2·64[k]	6·24	4·02	4·36	5·22	4·66	4·62	4·30	4·62	4·84
33*	6-OC_6H_5	0·827	3·43[k]	7·70	4·17	4·63	5·37	5·74	4·17	4·44	5·57	5·98
37	6-CF_3	0·550	2·70[k]	6·96	4·94	4·89	5·54	5·19	5·24	4·94	5·84	5·40
38	6-NO_2	0·215	1·77	6·64	4·01	4·49	4·61	4·96	4·61	4·93	5·21	5·15
46	5-F	0·374	2·20	6·27	4·37	4·44	4·57	4·68	4·97	4·60	4·97	4·87
50	5-CH_3	0·453	2·42	5·03	3·56	3·50	3·56	3·77	3·36	3·30	—[l]	3·90
60	3-F	0·356	2·15	6·33	3·97	4·48	4·57	4·73	—[l]	4·67	—[l]	4·91
61	3-CH_3	0·407	2·29	5·39	3·96	3·78	3·96	4·03	3·36	3·72	—[l]	4·18
62*	5,6-$(Cl)_2$	0·739	3·20	6·03	4·04	3·69	4·64	4·51	3·44	3·29	4·64	4·68

[a] Newly synthesized compounds are asterisked.
[b] Compounds described previously except for compound **62**, m.p. of which is 143–144°C.
[c] For three thiosalicylic acids, log *k'* and log *P* values were measured to formulate eqn (2). Substituent, log *k'*, and log *P* are: (6-Cl, 0·675, 3·29), (6-OC_6H_5, 1·127, 4·15) and (6-NO_2, 0·505, 2·72).
[d] *Echinochloa crus-galli.*
[e] *Polygonum convolvulus.*
[f] *Abutilon theophrasti.*
[g] By eqn (11).
[h] By eqn (13).
[i] By eqn (12).
[j] By eqn (14).
[k] Measured log *P* value.
[l] Not measured.

unsymmetric planar substituents such as CH_3CO and COC_6H_5, a similar set of $\mathbf{E_s}$ values can be estimated from their half-thickness and 'half-width' of the carbonyl side (2·48Å) and the opposite, using eqn (3).

For these π-bonded substituents, an experimentally derived $\mathbf{E_s}$ value is also available. From rate constants for acidic hydrolysis of *ortho*-substituted benzamides[13,14] and for the *N*-quaternization reaction of *ortho*-substituted *N*,*N*-dimethylanilines,[15] Sotomatsu and Fujita experimentally estimated the 'effective' $\mathbf{E_s}$ value for NO_2, C_6H_5, CH_3CO, CO_2CH_3, COC_6H_5, etc. In the present study, we used either one of the above mentioned $\mathbf{E_s}$ values depending upon the situation. For the 1-pyrryl group, the $\mathbf{E_s}$ value was taken as that of C_6H_5. The $\mathbf{E_s}$ value of the CH_3SO_2 group was estimated by regarding the van der Waals dimension for the 'half-width' as being represented by that of the SO side (2·86Å) with use of eqn (3). The reference point of the $\mathbf{E_s}$ values was taken as that of H whose $\mathbf{E_s}$ was defined as zero.

Of the STERIMOL parameters,[11,12,16] **L** is the length (Å) of substituents along the bond-axis connecting the α-atom to the rest of the molecule. $\mathbf{B_5}$ is the maximum width of substituents from the '**L**-axis' in the direction in which the longest chain of substituents extends in the fully extended (staggered) conformation. The references of these parameters were also shifted to that of H, so that they were denoted as $\mathbf{\Delta L}$ and $\mathbf{\Delta B_5}$, respectively.

For the electronic effect of substituents at the 5-position, the Hammett σ parameter was used.[11,17] For those at the 6-position, however, the 'proximity' electronic effect on the *ortho* carboxyl group[18] was examined with use of the Swain–Lupton **F** (field/inductive effect) parameter[19] corrected and extended by Hansch and coworkers.[11,17,20]

3 RESULTS

3.1 QSAR of ALS inhibitory activity

3.1.1 Effects of substituents at the 6-position in S-pyrimidinylthiosalicylic acids

In 6-substituted thiosalicylic acids (**1**–**18**) of Table 1, the activity varies markedly depending upon the substituent structure. The activity is highest in compounds with halogen atoms (**2**–**4**), CH_3 (**6**), SCH_3 (**12**), and CH_3CO (**17**). In the alkoxy (**7**–**9**) and alkylthio (**12**–**14**) compounds, the activity decreases with increasing length of the alkyl group. In halogeno compounds (**2**–**5**), the activity decreases with increasing atomic bulk as F > Cl > Br > I.

The potency variations seem to be dependent on the size or length of 6-substituents. The 6-substituents are also likely to exert steric promotion/retardation effects intramolecularly on the compulsory carboxyl group [mostly existing as the carboxylate ion under assay conditions because the pK_a value of this class of compounds was found in a range between 3·5 and 5·0. (Takeuchi, A., pers. comm.)] in the interaction with possible cationic receptor site(s). Thus, we examined various combinations of steric parameters. Among them, eqn (4) with $\mathbf{E_s}$ and $\mathbf{\Delta L}$ showed the best and most reasonable correlation. There is a significant colinearity between $\mathbf{\Delta L}$ and $\mathbf{\Delta B_5}$ parameters ($n = 15$, $r = 0{\cdot}937$) within the range of substituents included in the analysis. In fact, the use of $\mathbf{\Delta B_5}$ parameter gave a slightly poorer correlation, eqn (5). The colinearities of $\mathbf{E_s}$ value with $\mathbf{\Delta L}$ and $\mathbf{\Delta B_5}$ are much less significant, being $r = 0{\cdot}01$ and 0·08, respectively.

$$\begin{aligned} pI_{50} = &-0{\cdot}939(\pm 0{\cdot}409)(\mathbf{E_s})^2 - 1{\cdot}981(\pm 1{\cdot}016)\mathbf{E_s} \\ &- 0{\cdot}462(\pm 0{\cdot}170)\mathbf{\Delta L} + 7{\cdot}066(\pm 0{\cdot}544) \\ &n = 15,\ r = 0{\cdot}899,\ s = 0{\cdot}301,\ F = 15{\cdot}4 \end{aligned} \quad (4)$$

$$\begin{aligned} pI_{50} = &-0{\cdot}773(\pm 0{\cdot}443)(\mathbf{E_s})^2 - 1{\cdot}645(\pm 1{\cdot}087)\mathbf{E_s} \\ &- 0{\cdot}439(\pm 0{\cdot}187)\mathbf{\Delta B_5} + 7{\cdot}052(\pm 0{\cdot}607) \\ &n = 15,\ r = 0{\cdot}872,\ s = 0{\cdot}336,\ F = 11{\cdot}1 \end{aligned} \quad (5)$$

The addition of the terms for electronic parameters, σ_m or σ_p and **F**, singly or together did not improve the correlation in these equations. This does not necessarily mean, however, that the variations in the ALS inhibitory activity of thiosalicylic acids are entirely governed by steric conditions of the 6-position substituents. The value of the **F** parameter of 6-substituents for the 'proximity' electronic effect on the carboxylate group does not vary much, being located mostly around 0·3–0·5 except for that of H and CH_3 for which it is almost zero. If more compounds with alkyl and (alkyl)amino groups ($\mathbf{F} = 0{\cdot}0$–$0{\cdot}1$) are included additionally, the significance of the **F** (field/inductive) electronic effect term may be clearly shown.

In eqns (4) and (5), the $\mathbf{E_s}$ values for NO_2 and CH_3CO are those experimentally determined from the rates of hydrolysis of benzamides and quaternization of dimethylanilines, respectively. In the course of these reference reactions, the steric conditions of substituents are changed from those governed by the *ortho* carbamoyl and dimethylamino groups with the sp^2 hybridized 'central' atoms to those defined by sterically more congested sp^3 hybridized intermediate or final states. The fact that the carboxylate group in the 2-pyrimidinylthio-6-substituted benzoic acid structure is highly congested (to a degree greater than that in the corresponding salicylic acids) is not incompatible with the relevancy of the use of these 'experimental' $\mathbf{E_s}$ values. In other words, with a large buttressing steric effect of the 2-pyrimidinylthio group, the possible interaction of the carboxylate group with the action site(s) on the enzyme would suffer an intramolecular steric effect of 6-substituents of a type similar to that on the transition in the hybridization states in the above-mentioned reference reactions. Equations (4) and (5) indicate that, after the intermolecular-type steric effect is separated by the STERIMOL values, the optimum steric situation of 6-substituents for this intramolecular interaction is represented quantitatively about −1·05 in terms of the 'experimentally estimated' $\mathbf{E_s}$ value which is close to those of Cl, F, and alkylthio. The negative sign of $\mathbf{\Delta L}$ and $\mathbf{\Delta B_5}$ terms selects SCH_3 as the best among SR groups.

Most 6-alkoxy and alkylthio groups would exert their intramolecular steric effect with a geometry in which the congestion is minimized, so that the O and S atoms are faced to the carboxylate. The use of $\mathbf{E_s}$ values for these groups evaluated from the van der Waals radius of the O and S atoms is justified except for the $(CH_3)_2CHO$ and C_6H_5O substituents to formulate eqns (4) and (5). These two and the C_6H_5CO substituents were not included in the analyses. Their activity was much lower than that expected by these equations. A common feature of these three substituents is that they are branched at the β-position from the point of attachment. The β-branched structure could be significantly unfavorable for the interaction of the carboxylate with the possible enzymic active site(s).

3.1.2 Effects of substituents at the 6-position in O-pyrimidinylsalicylic acids

Effects of the 6-substituent of *O*-pyrimidinylsalicylic acids were analyzed with compounds (**19**–**45**) in Table 2. The substituent effects seem similar to those observed in the corresponding thiosalicylic acids, i.e. the halogeno (**21**–**23**) and SCH_3 (**34**) compounds show very potent activity. In this series, however, the C_6H_5O (**33**), C_6H_5 (**42**), and 1-pyrryl (**43**) compounds exert a remarkably high activity. The alkyl series compounds (**24**–**26**) show

rather low activity compared with the thiosalicylic counterpart (**6**).

Thus, the analyses with $\mathbf{E_s}$, $(\mathbf{E_s})^2$, and either one of STERIMOL $\mathbf{\Delta L}$ or $\mathbf{\Delta B_5}$ parameter terms were not enough to lead to an acceptable correlation, as apparent from eqn (6) and its counterpart with $\mathbf{\Delta L}$ in which the $\mathbf{E_s}$ and $\mathbf{\Delta L}$ terms are insignificant at the 95% level ($r = 0{\cdot}575$, equation not shown). The addition of the term for the 'proximity' electronic effect parameter **F** to eqn (6) improved the quality of the correlation considerably, resulting in eqn (7). The $\mathbf{\Delta L}$ counterpart was also much improved by the same operation but not enough, as shown in eqn (8).

$$\begin{aligned} pI_{50} = &-0{\cdot}456(\pm 0{\cdot}308)(\mathbf{E_s})^2 - 1{\cdot}196(\pm 0{\cdot}977)\mathbf{E_s} \\ &- 0{\cdot}351(\pm 0{\cdot}158)\mathbf{\Delta B_5} + 7{\cdot}112(\pm 0{\cdot}647) \\ &n = 24,\ r = 0{\cdot}801,\ s = 0{\cdot}439,\ F = 11{\cdot}9 \end{aligned} \quad (6)$$

$$\begin{aligned} pI_{50} = &-0{\cdot}532(\pm 0{\cdot}236)(\mathbf{E_s})^2 - 1{\cdot}262(\pm 0{\cdot}740)\mathbf{E_s} \\ &- 0{\cdot}328(\pm 0{\cdot}120)\mathbf{\Delta B_5} + 1{\cdot}721(\pm 0{\cdot}896)\mathbf{F} \\ &+ 6{\cdot}649(\pm 0{\cdot}547) \\ &n = 24,\ r = 0{\cdot}898,\ s = 0{\cdot}331,\ F = 19{\cdot}8 \end{aligned} \quad (7)$$

$$\begin{aligned} pI_{50} = &-0{\cdot}609(\pm 0.368)(\mathbf{E_s})^2 - 1{\cdot}339(\pm 1{\cdot}135)\mathbf{E_s} \\ &- 0{\cdot}192(\pm 0{\cdot}184)\mathbf{\Delta L} + 2{\cdot}110(\pm 1{\cdot}324)\mathbf{F} \\ &+ 6{\cdot}393(\pm 0{\cdot}794) \\ &n = 24,\ r = 0{\cdot}760,\ s = 0{\cdot}489,\ F = 6{\cdot}49 \end{aligned} \quad (8)$$

To derive eqns (6)–(8), we modified steric parameter values for some 6-substituents so that they could reflect their steric situation properly. As mentioned above, the congestion of the carboxylate in this series of compounds is lower than that in the thio analogs. The resonance within the carboxylate anion being predominant over that with the benzene ring, the rotation of carboxylate group could have a freedom to an extent greater than that in the thio analogs. The conjugation of NO_2 (**38**), CH_3CO (**40**) and COC_6H_5 (**41**) groups would be nearly normal, so that they are more or less coplanar with the benzene ring. The C_6H_5 (**42**) and 1-pyrryl (**43**) groups may be, however, twisted to a considerable extent greater than that in biphenyl.[21] In these situations, the NO_2, CH_3CO and COC_6H_5 groups would exert their steric effect on the carboxylate in the coplanar direction, so that their 'half-width' (of the shorter carbonyl side for CH_3CO and COC_6H_5 groups) is of importance. The situation for the sp^3 hybridized SO_2CH_3 group (**44**) could be similar, in that its steric effect is represented by the 'width' of the SO. For the C_6H_5 (**42**) and 1-pyrryl (**43**) groups being twisted much from the ring-plane, the steric effect could be expressed by their half-thickness. The $\mathbf{E_s}$ value used for these groups in eqns (6)–(8) was estimated from eqn (3) according to the above considerations. The alkoxy, alkylthio and amino groups were expected to show their effect from the side of O, S and N atoms, respectively, similar to the case of the thio analogs.

The above intramolecular steric conditions for the π-bonded planar substituents could be recognized by the size-limited cavity wall intermolecularly depending upon the STERIMOL values sometimes differing from those defined originally. Thus, for almost perpendicular C_6H_5 and 1-pyrryl substituents, the $\mathbf{\Delta B_5}$ values were taken to be those for the half-thickness in eqns (6) and (7). For almost coplanar NO_2, $COCH_3$ and COC_6H_5 groups, however, the original STERIMOL definitions were retained. For 24 compounds in eqns (6)–(8), the colinearity of $\mathbf{E_s}$ values with $\mathbf{\Delta L}$ and $\mathbf{\Delta B_5}$ are very low, being 0·05 and 0·21 (in r), respectively.

Equation (7) indicates that the optimum $\mathbf{E_s}$ value for the 6-substituent is about $-1{\cdot}18$, which is close to the values for those in highly potent compounds with substituents such as Cl (**21**), Br (**22**), SCH_3 (**34**), C_6H_5 (**42**) and 1-pyrryl (**43**). The optimum $\mathbf{E_s}$ value, $-1{\cdot}18$, is also close to that observed in eqns (4) and (5), although $\mathbf{E_s}$ values used for some specific substituents are different from those used in eqns (6)–(8). The positive **F** term indicates that the electron-withdrawing inductive and/or field effect of 6-substituents on the carboxylate group is indeed significant for potentiation of the inhibitory activity for the salicylic acids.

Contrary to the OC_6H_5 compound (**11**) in the thiosalicylic acid series, in which the OC_6H_5 substituent shows the β-branch effect to be detrimental to activity, the OC_6H_5 compound (**33**) was outlyingly very active in the salicylic acid series. This behavior was not accountable in the preliminary calculation. Thus, it was deleted from eqns (6)–(8). Some flexibility of the OC_6H_5 group around the C (salicylic 6-position)–O bond axis might be a factor to potentiate the activity. If the C_6H_5O group could rotate by 54° from the salicylic-benzene ring plane so that the '$\mathbf{\Delta B_5}$' value in the direction parallel to this ring plane is reduced to a half ('$\mathbf{\Delta B_5}$' = 2·45), the OC_6H_5 compound (**33**) could behave normally. Including this compound with this $\mathbf{\Delta B_5}$ value, the quality of the correlation of eqn (7) does not vary much ($n = 25$, $r = 0{\cdot}883$, $s = 0{\cdot}353$, $F = 12{\cdot}7$, equation not shown). With this conformation, no significant β-branch effect could be operative in the OC_6H_5 compound (**33**). The $(CH_3)_2CHO$ compound (**30**) was also not included. The detrimental β-branch effect seems to remain in the substituent of this compound. The CO_2CH_3 compound (**39**) was omitted because of a possible hydrolysis in the course of the inhibition reaction with the enzyme preparation.

3.1.3 Effects of substituent at the 5-position in O-pyrimidinylsalicylic acids

As shown in Table 3, the inhibitory potency of this

series of compounds (**46**–**58**) is lower than that of the unsubstituted (**19**), except for the 5-OH derivative (**59**). Compounds having such electron-donating substituents as NH_2 (**56**) and OH (**59**) and those with such small substituents as F (**46**) exhibit a higher inhibitory potency than those having such electron-withdrawing substituents as CN (**55**) and NO_2 (**58**) and such large substituents as OC_6H_5 (**53**).

Equations (9) and (10) with the 'ordinary' electronic σ and both ΔL and ΔB_5 STERIMOL parameter terms were formulated. Equation (9), with the term of σ_p representing the electronic substituent effect on the pyrimidinyloxy group, showed a better correlation. Equation (10) with the σ_m parameter in regard to the effect on the carboxyl group is slightly poorer. The ΔB_5 term in this equation is justified only at the 93% level. In accord with the qualitative discussions above, each of the σ, ΔL and ΔB_5 parameter terms is negative in these equations.

$$\begin{aligned} pI_{50} = &-1{\cdot}140(\pm 0{\cdot}824)\sigma_p - 0{\cdot}519(\pm 0{\cdot}439)\Delta L \\ &- 0{\cdot}354(\pm 0{\cdot}279)\Delta B_5 + 6{\cdot}284(\pm 0{\cdot}596) \\ n = 14,\ r = 0{\cdot}917,\ s = 0{\cdot}426,\ F = 17{\cdot}7 \end{aligned} \quad (9)$$

$$\begin{aligned} pI_{50} = &-1{\cdot}307(\pm 1{\cdot}306)\sigma_m - 0{\cdot}599(\pm 0{\cdot}486)\Delta L \\ &- 0{\cdot}279(\pm 0{\cdot}303)\Delta B_5 + 6{\cdot}515(\pm 0{\cdot}680) \\ n = 14,\ r = 0{\cdot}891,\ s = 0{\cdot}486,\ F = 12{\cdot}8 \end{aligned} \quad (10)$$

The OH compound (**59**) was omitted from these analyses, because the activity is much higher than that expected from eqns (9) and (10). The partial ionization of the OH group into the oxide ion, O^-, which is highly electron-donating ($\sigma_m = -0{\cdot}47$, $\sigma_p = -0{\cdot}81$)[11] may contribute to increasing the activity. Another possibility could be a hydrogen-donating hydrogen-bonding effect at this position.

3.2 Quantitative relationships between ALS inhibitory and herbicidal activities of *O*-pyrimidinylsalicylic acids

The relationships between in-vitro enzyme inhibition and the whole-body herbicidal activities were examined for substituted salicylic acids listed in Table 4 with which both in-vitro and in-vivo activities were accurately measurable.

The pre- and post-emergence herbicidal activities (pED_{90}) against a barnyard grass species, *Echinochloa crus-galli* (L.) Beauv., were analyzed with the pI_{50} value for the 'intrinsic' site-of-action activity along with log P value for the 'transport' behavior of compounds to give eqns (11) and (12).

Pre-emergence activity against *E. crus-galli*:

$$\begin{aligned} pED_{90} = &\ 0{\cdot}772(\pm 0{\cdot}295)pI_{50} + 3{\cdot}631(\pm 3{\cdot}542)\log P \\ &- 0{\cdot}778(\pm 0{\cdot}708)(\log P)^2 - 4{\cdot}619(\pm 5{\cdot}349) \\ n = 17,\ r = 0{\cdot}852,\ s = 0{\cdot}398,\ F = 11{\cdot}5,\ &\log P_{opt} = 2{\cdot}33 \end{aligned} \quad (11)$$

Post-emergence activity against *E. crus-galli*:

$$\begin{aligned} pED_{90} = &\ 0{\cdot}971(\pm 0{\cdot}252)pI_{50} + 3{\cdot}295(\pm 3{\cdot}054)\log P \\ &- 0{\cdot}810(\pm 0{\cdot}608)(\log P)^2 - 4{\cdot}812(\pm 4{\cdot}596) \\ n = 15,\ r = 0{\cdot}947,\ s = 0{\cdot}332,\ F = 31{\cdot}6,\ &\log P_{opt} = 2{\cdot}03 \end{aligned} \quad (12)$$

The coefficient of the pI_{50} term in the above correlation equation is very close or similar to unity, especially with consideration of the 95% confidence intervals. This suggests that the herbicidal activity corresponds almost in a one-to-one way with the ALS inhibitory activity when factors involved in the processes from the site of application to the site of action are separated by the log P and $(\log P)^2$ terms in spite of the fact that the plant species from which the ALS sample was prepared differs from that used for the herbicidal test. The significance of the terms of log P value for the neutral molecule indicates that it is the neutral form which could penetrate through a number of biomembraneous phases during the transport. The better quality of correlation in eqn (12) indicates that perturbation factors are less significant during the post-emergence than during the pre-emergence test. It is interesting to note that the optimum log P value is similar between pre- and post-emergence activities in spite of differences in the routes of uptake and translocation.

For broad-leaved weeds, analyses were made with the pre-emergence activity against *Polygonum convolvulus* L. and the post-emergence activity against *Abutilon theophrasti* L. Medic. giving eqns (13) and (14), respectively. In these equations, log P and its squared terms were not justified at the 95% significance level.

Pre-emergence activity against *P. convolvulus*:

$$\begin{aligned} pED_{90} = &\ 0{\cdot}740(\pm 0{\cdot}225)pI_{50} + 0{\cdot}043(\pm 1{\cdot}512) \\ n = 17,\ r = 0{\cdot}876,\ s = 0{\cdot}327,\ F = 49{\cdot}4 \end{aligned} \quad (13)$$

Post-emergence activity against *A. theophrasti*:

$$\begin{aligned} pED_{90} = &\ 0{\cdot}780(\pm 0{\cdot}261)pI_{50} - 0{\cdot}025(\pm 1{\cdot}810) \\ n = 15,\ r = 0{\cdot}883,\ s = 0{\cdot}245,\ F = 42{\cdot}6 \end{aligned} \quad (14)$$

Equations (13) and (14) indicate that the factors involved in 'transport' processes, including structural transformation mechanisms of this class of herbicide, are not significantly affected by substituent or structural variations in the broad-leaved plant body.

4 DISCUSSION

The above results indicate that the effects of variations in both the ALS-inhibitory and herbicidal activity of pyrimidinylsalicylic acids and their thio analogs is mostly rationalized by the physicochemical properties of substituents and molecules. At the receptor site(s), the benzene ring of these compounds is accommodated in a size-limited space. As shown in eqns (4)–(10), the size of substituents at the 5- and 6-positions on the benzene ring in terms of the STERIMOL length (**L**) and/or width ($\mathbf{B_5}$) is significantly limited for the higher ALS-inhibitory activity. The inhibitory activity of 3- and 4-substituted analogs was so low that pI_{50} values accurate enough for quantitative analyses were not available (data not shown). Thus, the size of substituents at these positions should be more severely limited for the proper binding of compounds.

The acidic carboxyl group is indispensable for ALS inhibition,[1] so it should be the carboxylate group which is responsible for the 'direct' binding of the inhibitor molecule with the catalytic site(s). Equations (4)–(8) indicate that, for the proper interaction of the carboxylate group, there is an optimal steric state for the 6-substituent, in each of the salicylate and thiosalicylate series. Being sandwiched by 2- and 6-substituents, the interaction of the carboxylate is also governed by the bulk of the bridge atom of the 2-position substituents, O or S. The carboxylate is more congested in the thiosalicylate compounds than in the corresponding salicylate derivatives. The $\mathbf{E_s}$ value of certain 6-substituents was differentiated between the two series, so that it can reflect the situations better as described above. In the salicylate series, the 6-C_6H_5 and 6-(1-pyrryl) compounds were those with steric substituent effect on the carboxylate close to the optimum. In the thiosalicylate series, however, the corresponding compounds were not so active as to give reliable inhibitory potency (data not shown), because the eventual steric effect of substituents was much higher than the optimum due to the greater congestion.

Although eqns (4) and (5) do not clearly show the participation of the electronic effect of 6-substituents in the thiosalicylate series, eqn (7) indicates its significance in the salicylate series. Equation (7) shows that the effect of the 6-substituents is electron-withdrawing in terms of the field/inductive **F** parameter, whereas eqns (9) and (10) indicate that the effect of the 5-substituents is electron-donating in terms of the ordinary Hammett σ, including not only the field/inductive but also the resonance effect. As described above, the **F** parameter term could be of significance in eqns (4) and (5) if the range of 6-substituents in terms of the **F** value is expanded. Therefore, eqn (7), and also eqns (4) and (5), indicate that the resonance effect of substituents is insignificant anyway in the activity of the 2,6-disubstituted benzoic acids series. This might be taken to mean that the π-bonded planar substituents, capable of resonance interaction with the ring, are twisted from the ring plane. The twisting is certainly insignificant, however, for symmetrical-top and mono-atomic substituents such as CF_3, CH_3 and halogens, even in these congested systems. Therefore, the insignificance of the resonance component in eqn (7) as well as (4) and (5) is not related to the twisting of the 6-substituents.

It is interesting to note that the dissociation constant in terms of pK_a for a series of di-*ortho* substituted benzoic acids has been analyzed[22] showing that the pK_a variations are not governed by the resonance component of the electronic effect of substituents, but by the field/inductive component in terms of the sum of σ_I values of two *ortho* substituents (which is almost equivalent with that of the **F** values for the corresponding substituents) along with their steric effect. A similar electronic effect has been found[23] in the analysis of the carbonyl stretching frequency in the IR spectrum of a series of 2,6-disubstituted benzamides. The stretching frequency varies depending on the sum of σ_I values of two *ortho* substituents with no significant participation of their resonance effect. In the QSAR analyses of the di-*ortho* substituent effect in the 1-(2,6-disubstituted benzoyl)-3-phenylureas on the larvicidal activity,[24] only the field/inductive component is significant as the electronic effect of di-*ortho* substituents. These examples suggest that the through-bond electronic effect is not significant but the through-space type effect of di-*ortho* substituents is important in physical-organic as well as bioactive compound systems for congested 2,6-disubstituted benzoyl compounds.

For the *O*-pyrimidinylsalicylic acid series in which the electronic effects of both 6- and 5- position substituents were analyzed, the most plausible elucidation of overall electronic effect of substituents could be as follows. The through-space electron withdrawal of the 6-substituents would attract the electron flow toward the carboxylate ion. The through-bond electron-donating effect of the 5-substituents would increase the electron density at the carboxylate ion. Thus, the net electronic effect of substituents would be to elevate the electron density of the carboxylate ion, which could in turn intensify the interaction with the anionic receptor site(s). In this respect, eqn (10) would be the equation which illustrates the effect of the 5-substituents more appropriately in spite of the quality of the correlation being slightly poorer than that of eqn (9).

Recently, Andrea *et al.*[25] analyzed QSAR in detail for the ALS-inhibitory activity of sulfonylurea derivatives with prominent herbicidal activity. From their results, those with use of data sets including a relatively large number of compounds are cited here. For the ALS inhibitory activity of 2-substituted-benzenesulfonylureas (**III**: X at the 2-position in Fig. 2), they formulated eqn (15).

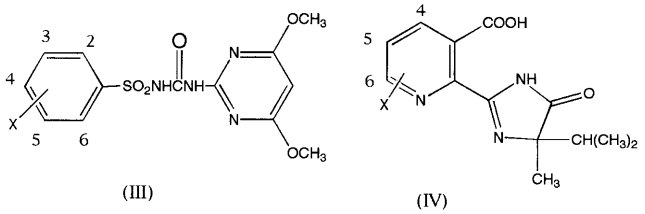

Fig. 2. The general structures of sulfonylureas (**III**) and imidazolinyl-pyridine-3-carboxylic acids (**IV**).

$$\begin{aligned} pI_{50} &= 0{\cdot}385(\pm 0{\cdot}157)\pi + 0{\cdot}222(\pm 0{\cdot}055)\mathbf{MR} \\ &\quad - 0{\cdot}0079(\pm 0{\cdot}0016)(\mathbf{MR})^2 \\ &\quad + 0{\cdot}830(\pm 0{\cdot}692)\mathbf{F} + 6{\cdot}554(\pm 0{\cdot}451) \\ n &= 39,\ r = 0{\cdot}898,\ s = 0{\cdot}381,\ \mathbf{MR}_{opt} = 14{\cdot}05,\ F = 35{\cdot}4 \end{aligned} \tag{15}$$

For 5-substituted-2-carbomethoxy-benzenesulfonylureas (**III**: X = 2-CO_2CH_3, 5-variable in Fig. 2), eqn (16) was given.

$$\begin{aligned} pI_{50} &= 0{\cdot}253(\pm 0{\cdot}150)\pi - 0{\cdot}036(\pm 0{\cdot}0164)\mathbf{MR} \\ &\quad - 0{\cdot}924(\pm 0{\cdot}359)\sigma_p + 7{\cdot}750(\pm 0{\cdot}261) \\ n &= 17,\ r = 0{\cdot}945,\ s = 0{\cdot}195,\ F = 36{\cdot}2 \end{aligned} \tag{16}$$

In eqns (15) and (16), π is the hydrophobicity parameter and **MR** is the molecular refractivity of variable substituents. Although eqn (16) uses the ordinary σ_p constant with respect to the 2-CO_2CH_3 group, the general pattern of the QSAR resembles that of the *O*-pyrimidiny salicylates. Equation (15) indicates that the substituents *ortho* to the SO_2N^- group, ionized under assay conditions, exert an electron-attracting field effect. Equation (16) suggests an electron-donating *meta* substituent effect on the SO_2N^- group, since the colinearity between σ_p and σ_m for 17 substituents is quite high ($r = 0{\cdot}89$). The higher the electron density of the SO_2N^- ion, the higher is the inhibitory activity. There is an optimum steric circumstance for the sulfonamide anion to interact with the cationic action sites in terms of **MR** of the *ortho* substituents in this series.

Cross and Ladner[26] analyzed the QSAR of another well-established series of ALS-inhibitory herbicides, i.e. the 2-imidazolinyl-pyridine-3-carboxylic acids (**IV**, Fig. 2). For the post-emergence herbicidal activity of a series of the 5-X compounds (**IV**: X at the 5-position) in terms of pED_{90} against the hedge bindweed (*Calystegia sepium*, L.), eqn (17) was formulated.

$$\begin{aligned} pED_{90} &= -3{\cdot}70(\pm 2{\cdot}16)\sigma_p - 0{\cdot}31(\pm 0{\cdot}15)\mathbf{L} + 1{\cdot}84 \\ n &= 11,\ r = 0{\cdot}90,\ s = 0{\cdot}39,\ F = 16{\cdot}59 \end{aligned} \tag{17}$$

Equation (17) is not inconsistent with our present results or with eqn (16) for the sulfonylurea herbicides. The introduction of substituents into the 6-position of the pyridine-3-carboxylic acids (**IV**) generally reduces herbicidal activity. This seems also in accord with the finding with salicylates in which the 4-position corresponds with the 6-position of the pyridine-3-carboxylic acids (**IV**).

As described in the preceding section, factors related to structural transformations such as metabolic detoxications did not show up explicitly in eqns (11)–(14) for herbicidal activity. This does not necessarily mean that no structural transformation occurs during the 'transport' processes. If the site of transformation in the molecule is far apart from the salicylic acid-benzene ring, no substituent or structural variation effect would be of significance on the metabolic detoxication. In fact, the site where the metabolic detoxication occurs in the closely related series of compounds has been shown to be one of the two methoxy groups on the pyrimidine ring[27] on which the effect of substituent variations in the salicylic moiety does not work without significant attenuation.

In conclusion, the effects of substituents at the position *ortho* to the carboxyl group in the two series of ALS inhibitors are complex. This is especially so because the compulsory carboxyl group is sandwiched between two *ortho* substituents. Although significant correlation equations were formulated for the *ortho* substituent effects, it was necessary to modify original definitions of steric parameters for certain substituents, depending on the 2-position bridge atom, O or S. Thus, the present analyses should be validated further by compound series including systematically designed substituent sets, perhaps with compounds multiply substituted at the 6- and other positions simultaneously. Comparison of the QSAR results with those for other structural series of ALS inhibitors such as sulfonylureas and imidazolinyl-nicotinic acids having systematically introduced substituents would be invaluable to understand the structure–activity pattern of these important classes of herbicides.

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